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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/577,897	05/24/00	HORVITZ	H 01997/198007

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EXAMINER	
SHUKLA, R	
ART UNIT	**PAPER NUMBER**
1632	5

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/577,897	Applicant(s) HORVITZ ET AL.	
	Examiner Ram Shukla	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,6,16 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,6,16 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply* .

DETAILED ACTION

1. Claims 5, 6, 16, and 19 are pending in the instant application.

2. **Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.**

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Specifically the application fails to comply with CFR 1.821(d), which states:

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing " in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

It is noted that figures 3 contains several sequences of 12 amino acids, however, these sequences are not identified by sequence identifiers. Likewise, figure 7 discloses three different sequences, however, it is not clear if these sequences are listed in the sequence listing, because brief description of these figures does not identify these sequence with sequence identifiers. Likewise, figure 7 discloses three different sequences, however, it is not clear if these sequences are listed in the sequence listing, because brief description of these figures does not identify these sequence with sequence identifiers.

It is further noted that the specification does not contain a CRF and a paper copy of the sequence listing. Since the application is a divisional of 08/984,178 which is a continuation of 08/287669, applicants can submit a paper copy of the sequence and request the transfer of the CRF from the parent application.

For compliance with sequence rules, it is necessary to include the sequence in the "Sequence Listing" and identify them with SEQ ID NO. In general, any

sequence that is disclosed and/or claimed as a sequence, i.e., as a string of particular bases or amino acids, and that otherwise meets the criteria of 37 CFR 1.821(a), must be set forth in the "Sequence Listing." (see MPEP 2422.03).

For the response to this office action to be complete, Applicants are required to comply with the Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Specification

3. Pages 1-17, 19-29, 31, 33-41, 43, 45 on line 31 or 33 have an overprint at the beginning of the line. It is not clear if the letters are relevant to the specification or it is typographical error. Appropriate corrections are required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 5, 6, 16, and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated ced-3 protein from a nematode, wherein the nematode is a Caenorhabditis elgans, C.briggsae, and C.vulgaris and wherein the protein is encoded by a ced-3 nucleic acid of a Caenorhabditis elgans, C.briggsae, or C.vulgaris, does not reasonably provide enablement for an isolated protein encoded by any and all ced-3 nucleic acids, a hydrophilic and serine rich region containing protein encoded by a nucleic acid structurally related to the ced-3 nucleic acid of SEQ ID NO 18 or a protein encoded by a nucleic acid that is functionally related to the ced-3 nucleic acid wherein the protein encoded by the nucleic acid causes cell death and a protein encoded by a

nucleic acid that is both structurally and functionally related to the ced-3 nucleic acid or any other embodiments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The specification is not enabling for the claimed invention because the specification does not provide sufficient guidance as to how an artisan would have made and used the claimed invention commensurate with the braod scope of the claims and artisan of skill would have required extensive experimentation to make and use the claimed proteins and such experimentation would not have been considered routine for an artisan of skill and therefore, such experimentation would have been considered undue, as discussed below.

The instantly presented invention as claimed encompasses ced-3 proteins from any source encoded by any and all wild type and mutant ced -3 genes, genes

that are structurally and functionally related to ced-3 or that can cause cell death, as measured in an in vivo or in vitro bioassay, from any and all organisms including microbes, invertebrates, vertebrates and plants (see pages 2 and 3 of specification). First, the issue is what would be encompassed by a ced-3 nucleic acid which would encode a protein? It is noted that the specification discloses a ced-3 nucleic acid in Seq ID No 18 that encodes the amino acid sequence of Seq ID No 19 and ced-3 alleles that have mutations in certain sites listed in table-3 (see page 62 of the specification). The specification does not disclose as to what kind of genes or nucleic acid sequences would encompass a ced-3 gene. The specification does not teach as to what characteristics would have been required of a protein to be called a ced-3 protein or what characteristics a nucleic acid should have to be called a ced-3 nucleic acid. For example, what kind of sequence similarity or identity between the ced-3 (SEQ ID NO 18 or 19) would qualify a nucleic acid or protein to be called a ced-3 nucleic acid or protein. Accordingly, an artisan of skill would not have known how to determine whether a nucleic acid was a ced-3 nucleic acid. It is noted that the specification on page 48 discloses how to isolated alleles of ced-3 from C.elegans, however, it does not provide any guidance as to what characteristics a nucleic acid should have that would be called a ced-3 nucleic acid, not any thing else. Furthermore, it is noted that the effective filing date for the instant application is 1992 and at the time of the invention, only ced-3 in the prior art or the specification known was in C.elegans. In other words, an aritsan of skill would not have known how to make a ced-3 nucleic acid or protein from any other organism (see discussion in later paragraphs). Next the issue is: what is considered structurally related to the ced-3 nucleic acid of SEQ ID NO 18? The specification on page 13, lines 15-25 describes sructurally related genes to genes that have some nucleotide similarity. Likewise, functionally related have been described as those that cause cell death activity. However, an artisan would not have known how to make and use proteins based on some nucleotide similarity or protein sequence similarity in the absence of any degree of similarity. It is recognized in the prior art that the function of a protein depends on the sequence

of its amino acids in a certain pattern, conformation of the protein due to the amino acid sequence, and the functional properties of the different parts of the protein (see second paragraph in Rudinger J in Peptide Hormones. Editor Parsons JA. Pages 1-7, 1976, University Park Press, Baltimore). Rudinger further add, "The significance of particular amino acids and sequences for different aspects of biological activity can not be predicted *a priori* but must be determined from case to case by painstaking experimental study" (see conclusion on page 6). The specification does not teach which changes in the nucleotide sequence of SEQ ID NO 18 would yield a nucleic acid that would be structurally similar to nucleic acid of SEQ ID NO 18 and would encode a amino acid sequences that would retain the function of the human ced-3 protein of SEQ ID NO 19. The specification does not teach how to use a nucleic acid that would have encoded a protein which was encoded by a nucleic acid that was similar to SEQ ID NO 18 but did not have the function of the protein of SEQ ID NO 19. Alternatively, the specification does not teach how would an artisan have made or used protein that was encoded by a polynucleotide that was similar to SEQ ID NO 18 but in which the nucleic acids were extensively changed.

As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

It is noted that every nucleic acid is a hydrophilic in nature, therefore, an artisan would not know as to how to differentiate a hydrophilic nucleic acid that

encodes a ced-3 protein from another hydrophilic nucleic acid that does not encode a ced-3 protein.

Furthermore, the specification does not teach whether any and all organisms other than Caenarhabditis would have a ced-3 gene, or whether even all the nematodes would have a ced-3 gene. At the time of the invention, Driscoll et al (TINS 15:15-19, 1992), while reviewing the state of the development and abnormal cell death in C.elegans, noted that the pressing issue at that time was to establish whether mechanistically similar deaths occur in other species. They further noted that although programmed cell and degenerin induced death in C.elegans resembled apoptosis and necrosis, classification based solely on morphological comparisons may be an oversimplification, underlying molecular details leading to death need to be resolved (see first full paragraph in the left column on page 19). In other words, at the time of the invention, state of the art of programmed cell death did not teach ced-3 related genes in other organisms. Therefore, an artisan would have depended on the specification to make and use proteins encoded by ced-3 nucleic acids from other organisms. However, the specification does not teach as to how an artisan of skill would have made a proteins or the nucleic acids that encoded the claimed proteins, encompassed by the claimed invention, from any and all living organisms? Even if one had to assume that using various screening and other molecular biology techniques described in the specification and available in prior art, an artisan would have been able to isolated a DNA that encoded a protein as encompassed by the claimed invention, an artisan would not be able to know whether the proteins would have a specific functions or a cell death activity? It is noted that the specification teaches bioassay using C.elegans, however, neither the specification nor the prior art teaches that a protein that may produce cell death in C.elegans would also produce cell death in another organism. The difference between the programmed cell death mechanism in C.elegans and other organisms was also emphasized by Freeman et al (Current Opinion in Neurobiology 3:25-31, 1993) who noted that compared to C.elegans, where the loss of a single gene, ced-3 or ced-4 resulted in failure of all cell death, in higher

species, where a multitude of physiological deaths are necessary for survival, redundant pathways may have evolved, which may indicate that elimination of a critical component of one pathway may have little or no effect on the death of a particular cell., that is not a Caenorhabditis. It would further raise the issue whether different living organisms would have a ced-3 gene or even if they do have, would the proteins encoded by these genes be same in all the organisms or would they have same function or would require similar cofactor? Furthermore, the specification does not disclose whether even all the nematodes would have a ced-3 gene. It is noted that the phylum nematoda contains 12,000 species which not only have different body structure, size, physiology, they may be free living or parasite (see pages 509-515 in chapter 24 of General Zoology, editors: Villee et al, Saunders College Publishing, New York, 1984). Therefore, based on the teachings of the art, it is not clear whether the results obtained in C.elegans would be representative of any and all nematodes. In other words, the in vitro or in vivo bioassay system of ced-3 mutant C.elegans may not be useful in determining the biological activity of a protein that was functionally related to ced-3. Therefore, an artisan would have to develop assay system to test the claimed proteins of the instant application. The specification does not provide any guidance as to how an artisan would have determined what would have been the function of all these polynucleotides and how would these multitude of polynucleotide would have been used or for what use.

It is concluded that the specification as filed is not enabling for the claimed invention as filed and an artisan would not have been able to practice the invention without undue experimentation. Therefore, limitation of the scope of the invention to an isolated ced-3 protein from a nematode, wherein the nematode is a Caenorhabditis elgans, C.briggsae, and C.vulgaris and wherein the protein is encoded by a ced-3 nucleic acid of a Caenorhabditis elgans, C.briggsae, or C.vulgaris, is proper.

6. Claims 1, 4, 8, 15, 17, 18, 22, 33, 35, 36, and 40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is referred to the revised interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-111 (also available at www.uspto.gov).

When the claims are analyzed in light of the specification, instant invention encompasses ced-3 proteins from any source encoded by any and all wild type and mutant ced -3 genes, genes that are structurally and functionally related to ced-3 or that can cause cell death, as measured in an in vivo or in vitro bioassay, from any and all organisms including microbes, invertebrates, vertebrates and plants. However, the specification discloses only a protein disclosed in SEQ ID NO 19 that is encoded by the nucleic acid disclosed in SEQ ID NO 18. The specification also discloses alleles of ced-3 that have mutations at certain amino acid residues. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, SEQ ID NO 19 is the only species whose complete structure is disclosed. The specification does not provide any disclosure as to what would have been the amino acid sequence of ced-3 or nucleic acid of ced-3 of other animal species or even nematodes. The specification does not provide any guidance as to how related nucleic acids encoding ced-3 of different animal species would be related to each other.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other identifying characteristic are the nucleotide sequence, that the sequences are similar to ced-3 and that the nucleic acids are hydrophilic and that the protein has

serine rich regions. However, these two characteristics are not specific to ced-3 since all the nucleic acids are hydrophilic and a multitude of proteins have serine rich regions. In regard to polynucleotides from species other than humans, it is noted that the specification does not provide any disclosure whether these sequences from other species would have had same characteristics would have had additional characteristics or properties.

This limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of the ced-3 protein sequence of besides Seq ID No 19 and that is encoded by the nucleic acid sequence disclosed in SEQ ID No 18, and variants of SEQ ID NO 18 at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-4, 8-15, 17, 18, 21, 22, 25, 33, 35, 36, and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5 and 6 are indefinite because these claims define the claimed protein by a name only. Reference of a nucleic acid by name is indefinite and unclear because any other nucleic acid can be given a certain name irrespective of its function and structure. To clearly identify a certain nucleic acid, it should be characterized by its sequence, protein made, functional activity and characteristics of the protein.

Claim 19 is indefinite because they recite the phrase "structurally related" and "functionally related", however these phrases are not clearly defined in the specification. For example, in relation to structurally related in terms of sequence,

what is the degree of relatedness. Likewise, what functions and to what degree a given gene is related to claimed gene.

Claim 6 is indefinite because figure 4 is discloses a nucleic acid as well as a protein sequence, however, claimed invention and SEQ ID NO 19 are directed to an amino acid sequence and therefor figure 4 is not a true representative of the invention being examined.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 5, 16, and 19 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Yuan (1990)(listed in the IDS submitted 9-19-00).

Yuan teaches DNA cosmids that contain the ced-3 locus and a DNA fragment of 12 KB which restores the ced-3 phenotype when injected in a ced-3 mutant (see last two sentences on page 203 and last paragraph on page 211 continued in first paragraph on page 213 in chapter 4). Accordingly, this fragment would encode the ced-3 protein. Yuan also teaches alleles of ced-3 (see page 204-207) which were also tested in C.elegans for complementation. Furthermore, Yuan teaches multiple cosmids that would have overlapping parts of ced-3 which were used in the biological assay using C.elegans ced-3 mutants. Accordingly, these cosmids would be structurally and functionally similar to ced-3. It is noted that Yuan does not teach SEQ ID NO 18, however, since the instant application does not describe how similar nucleic acid has to be to SEQ ID NO 18, any ced-3 nucleic acid would be considered similar to SEQ ID NO 18 and thus their encoded protein would anticipate invention of claim 19. Therefore, Yuan anticipates the protein of claims 5, 16, and 19.

It is noted that Yuan does not amino acid sequence, however, since the ced-3 nucleic acids were tested in complementation assays using ced-3 mutant C.elegans, when these nucleic acids complement the mutants, a protein would be encoded and therefore, the encoded protein will be considered an inherent property of the ced-nucleic acids of Yuan. Thus, the claimed invention as a whole was at least prima facie obvious over, if not anticipated by, the prior art. In the event that the claimed proteins are not identical to those encoded by the nucleic acid of Yuan, it is considered that any differences would be result of minor variations, wherein such variants would have been obvious over the prior art.

11. The isolated protein disclosed in SEQ ID NO 19 is free of the prior art of record.

12. No claim is allowed.

Applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c) and a copy of all the pending/under consideration claims. For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Kay Pinkney whose telephone number is (703) 305-3553.

Ram R. Shukla, Ph.D.

RAM R. SHUKLA, PH.D
PATENT EXAMINER